

Remarks*Sequence Compliance*

The Examiner notes that Fig. 3 contains sequences not identified by SEQ ID NOs. Applicants enclose herewith a complete set of formal drawings, wherein only Fig. 3 has been amended to identify the sequences listed therein by their sequence identifier number. In compliance with 37 C.F.R. 1.821-1.825, Applicants further enclose herewith a new sequence listing in computer readable format and a paper copy, along with a statement that the paper and electronic copies are the same.

Specification

Applicants have amended the specification as requested by the Examiner to specify that international application PCT/CA97/00892 and USSN 09/318,106 are abandoned. Minor typographical errors have also been corrected by amendment. No new matter is added by these amendments and there entry is respectfully requested.

Claim Rejections

- I. Claims 27-32 were rejected under U.S.C. §112, first paragraph.

The Examiner contends that the state of the art indicates that animal models for restinosis, including the commonly used rabbit, rodent and porcine models, are not predictive of function in humans, and thus, the skilled artisan would encounter [state of art] teachings that indicate the unpredictable and difficult nature of the claimed invention and would not be able to turn to prior art for assistance in practicing the method for its real world use.

The Applicants respectfully disagree and request that the rejection be withdrawn for the following reasons.

To establish this view of the state of the art, the Examiner has relied solely on a single reference, O'Sullivan *et al.* Applicants respectfully submit that the assessment of the state of the art does not consist of one authors opinion, but rather consists of the global

view of skilled artisans. The Applicants submit that in the present invention, they have used the animal model most widely accepted in the field. O'Sullivan et al., may not like the model, but it remains that the animal model used by the Applicants is the most widely accepted. O'Sullivan's view of the state of the art is based on his own personal view of the utility of the animals as models for gene therapy and not their utility as models of intravascular disease. In fact, O'Sullivan's view is not supported by any scientific reference in the article.

The Examiner is assessing the "state of the art" of animal models for use in the filed of gene therapy as being unpredictable. In the present application, there is no gene therapy in the pure meaning of gene therapy, for there is no healing of a disease by the introduction of a functional gene. The inventors have invented a way of attaching medication to an oligonucleotide or any other intravascular device such as a stent and deliver the medication. There is no gene therapy *per se*. Therefore, the art relevant to the present invention is the art of intravascular disease, which widely accepts the animal model used by the Applicants, not the gene therapy art.

In addition, the Applicants respectfully disagree with the Examiners statement that O'Sullivan indicates "that injuries sustained in the models are not considered to be correlated to injuries that are sustained in humans". Referring to the validity of animal models in order to reproduce human disease O'Sullivan stated: "we cannot be certain that this is the case", which can be easily replaced by the exact opposite statement: we cannot be certain that this is **not** the case (page 1, lines 1-4). Further, it is a standard with the porcine models to sacrifice the animals after 28 days. This time period may be prior to the onset of restenosis in humans, but it is not prior to the onset in porcine. Animal models often have different "timelines" than humans, and such a difference certainly does not negate their utility as a models for disease.

The Examiner contends that the Applicants have provided *in vivo* data concerning the invention only with regards to an animal (porcine) model and that when practicing the instant invention, the skilled artisan would be unable to turn to the instant specification for guidance because there is no indication of its function in humans by way of direct results, or by provision of functional correlation between animal data and human

application.

Applicants respectfully disagree. The Examiner is requiring **clinical and therapeutic efficacy**, which is **not the standard** that is to be used in the PTO. *In re Brana*, 51 F.3d 1560, 1568, 34 USPQ 2d 1437 (Fed. Cir. 1995). Further, reduction to practice of a patentable invention does not require that the invention be in a commercially satisfactory stage of development, *Scott v. Finney*, 34 F.3d 1058, 32 USPQ 2d 1115 (Fed. Cir. 1994).

As stated above, the Applicants have used an animal model widely accepted in the field. The Examiner is basing the position set forth in the office action on O'Sullivan's view of the validity of animals as models for human disease. This represents one persons view of the art. Further, if one were accept the position set forth in the office action, then every single patent in the field of medicine that used an animal model to demonstrate the potential beneficial effect of a new drug could be contested, since there is not a single animal model (other than human) that can really represent the human system. Since drugs can not be tested on humans before animal trials, and in order to have a commercial incentive, patents must be applied for before human clinical test, animal models have been and must continue to be accepted by the USPTO.

Applicants respectfully submit that, in addition to the specification as a whole, specific examples are provided wherein the applicants demonstrate the working principles of the present invention by using a well established animal model, which give ample support for the method of the invention to treat restenosis, see Example II. Applicants have used the porcine coronary overstretch injury model of restenosis. This is a model recognized by experts in cardiovascular research as a vascular injury model that resembles the injury of human angioplasty. See, "Consensus Report" Attachment A. In fact, the model has been accepted by the USPTO as at least one recent patent (2002) has issued claiming treatment of restenosis in which the supporting data was generated using the porcine coronary overstretch model. See, Attachment E, USP 6,468,297

The Examiner contends that the level of the skill in the art concerning using internally radiolabeled oligonucleotides for inhibition of restenosis in humans is highly underdeveloped.

Applicants respectfully disagree. Applicants point out that when rejecting claims for enablement, the level of skill of the artisan, not the level of development in the art should be assessed. The skilled artisan in this art is a specialized clinician (cardiovascular surgeon), and thus the level of the skilled artisan would be high. One skilled in the art would thus readily understand the description and the claims of the instant application.

The Examiner contends that the art is highly unpredictable, as demonstrated in the “state of the art”, where O’Sullivan indicates that porcine models are not indicative of function in humans. The Examiner further takes the position of additional areas of unpredictability such as a) toxicity of the oligonucleotides, b) effective targeting of oligonucleotides, and c) long-term effects of oligonucleotides.

Applicants submit that, as indicated above, the O’Sullivan reference does not represent the “state of the art” with respect to the utility of restenosis animal models. Thus basing a view of unpredictability on O’Sullivan is erroneous. With respect to the Examiners’ view that the use of oligonucleotides is unpredictable as to their toxicity, effective targeting of, and long term effects of, the Applicants respectfully disagree.

Applicants describe throughout the Specification methods for local delivery of radiolabeled oligonucleotides at the site of angioplasty, such as directly or indirectly attaching oligonucleotides to a stent surface, or by catheter delivery, see for example the Specification at page 20, lines 13-16, page 21, lines 15-19, and Example II on page 25, lines 5-30, which specifically describes the local drug delivery procedure used in the restenosis porcine model. Thus, the Applicants have clearly provided means for effective targeting.

With regards to the toxicity and long term effects of the oligonucleotides, Applicants respectfully submit that this burden above and beyond the requirements of the PTO standards and appears to be requiring long term clinical studies. Applicants respectfully submit that reduction to practice of a patentable invention does not require that the invention be in a commercially satisfactory stage of development, *Scott v. Finney*, 34 F.3d 1058, 32 USPQ 2d 1115 (Fed. Cir. 1994).

Although an argument is not necessitated, because clinical and therapeutic efficacy is not the standard of the PTO, Applicants point out that toxicity of ³²P oligonucleotides

has been assessed in monkeys. In monkeys, doses at 2 mg/kg caused no major cardiovascular changes. In the case of the ^{32}P -labeled oligonucleotide, the amount of oligonucleotide associated to 1 mCi is in the order of 50 μg . If the mean weight of a human is estimated to be 70 kg and a safe dose of 2 mg/kg would correspond to 140 mg of oligonucleotide, then a dose of 1 mCi of ^{32}P -oligonucleotide would contain **2800 time less oligonucleotide than the safe dose**. See, Black et al., Attachment D.

With respect to the on the time of sacrifice of the animals, Applicants respectfully submit that the 28 days to sacrifice, it is a standard with the porcine models. By 28 days, the control group in which the stenosis is provoked, the neointima is fully developed and very similar to the one found in human. See, Kornowski et al., Attachment B; Herman et al., Attachment C. The examiner should also note that the 3 to 6 month period that is associated with restenosis corresponds to the peak of reocclusion which does not mean that reocclusion could not happen before 3 months.

In addition, numerous subsequent studies relating to the use of radioactivity to treat restenosis support that the present invention with respect to the use of radioactivity to treat restenosis is safe and feasible.

The Examiner contends that there is a great deal of trial and error experimentation associated with the instant invention stating that 1) "there needs to be a bona fide correlation between invention and its effectiveness in humans, either by experimental data or by clear indication that the animal model is predictive" and 2) "and the toxicity, targeting and long term effects of the treatment need to be clearly established..."

Applicants respectfully disagree. Again, the examiner is taking one authors the view that the animal model used by the inventors is not predictive. Applicants respectfully disagree. The porcine model of the present invention has been widely used. O'Sullivan himself even stated that the animals models of vascular injury that most closely resemble the injury of human angioplasty are porcine coronary overstretch injury (which the inventors used) and coronary angioplasty in the non-human primates (Page 2, lines 4-5). Again, a committee of recognized experts in cardiovascular research has proposed a set of standards to evaluate drug eluting stents that involved using the overstretched artery in a

porcine model, providing recognized utility of the model. See, Attachment A. In fact, as noted above, the model has been accepted by the USPTO as at least one recent patent (2002) has issued claiming treatment of restenosis in which the supporting data was generated using the porcine coronary overstretch model. See, Attachment E, USP 6,468,297

With respect to the Examiners contention that the toxicity, targeting and long term effects of the treatment need to be clearly established, as submitted above, this is not the standard required by the PTO.

In light of all of the above, the Applicants respectfully request that the rejection of claims 27-32 under U.S.C. §112, first paragraph be withdrawn.

II. Claims 27-32 were rejected under U.S.C. §112,, second paragraph .

Applicants submit that the amendment of claim 27, as suggested by the Examiner, to recite "DNA sequence conjugated to an antibody" rather than "DNA sequence bounded to an antibody" has obviated the rejection.

Applicants respectfully request that the rejection of claims 27-32 were rejected under U.S.C. §112,, second paragraph be withdrawn.

In view of the above and foregoing, it is respectfully submitted that the claims now on file are believed to be in condition for allowance, and prompt and favorable action is earnestly solicited. Should there be any question concerning this response or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Authorization is hereby given to the Commissioner to charge any deficient fees or to credit any overpayment to account no. 50-0850.

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Respectfully submitted,

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